Published in final edited form as:

Dermatol Surg. 2014 December ; 40(12): 1390–1394. doi:10.1097/DSS.000000000000183.

A Prospective Study of Pain Control by a Two-Step Irradiance Schedule During Topical Photodynamic Therapy of Non-melanoma Skin Cancer

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Abstract

Background—Topical photodynamic therapy (PDT) for selected non-melanoma skin cancer, employing 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) has yielded high long-term complete response rates with very good cosmesis. Pain during light activation of the photosensitizer can be a serious adverse event. A two-step irradiance protocol has previously been shown to minimize ALA-PDT pain.

Objectives—To determine the irradiance-dependent pain threshold for MAL-PDT, to adapt the two-step protocol to an LED light source, and assess clinical response.

Methods—In this prospective study, 25 superficial basal cell carcinoma (sBCC) received an initial irradiance by laser at 40 or 50 mW/cm², or LED at 35 mW/cm² followed by an irradiance at 70 mW/cm² for a total of 75 J/cm². Pain levels were recorded for both irradiance steps. Efficacy was assessed at 6, 12 or 24 months.

Results—Pain was mild in the 40/70 mW/cm² laser cohort. Three instances of irradiance-limiting pain occurred at 50/70 mW/cm². Pain was minimal in the 35/70 mW/cm² LED cohort. Clinical response rates were 80% in the 50/70 mW/cm² laser cohort and 90% in the 35/70 mW/cm² LED cohort.

Conclusions—Topical PDT can be effectively delivered to sBCC with minimal treatment related pain by a two-step irradiance protocol.

Introduction

Photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) or its derivatives, which upon application leads to the production and accumulation of the photosensitizer protoporphyrin IX (PpIX) in the lesion to be treated, has become an accepted standard approach for treating actinic keratoses (AK) and selected basal cell carcinomas (BCC)¹⁻³. While achieving high durable response rates and excellent cosmetic outcomes, the pain experienced during light delivery can be a significant limiting factor of this therapy⁴⁻⁸. Various pain-relieving approaches have been used with limited success^{9;10}. A novel approach towards pain control during ALA-PDT has recently been introduced. The method employs a two-step irradiance protocol, i.e. initial laser irradiation at low irradiances (10-60 mW/cm²) until 90% of the initial PpIX is photobleached, as determined by surface fluorescence measurements, with a subsequent increase of the irradiance to 150 mW/cm² for a total light dose of 200 J/cm². This two-step scheme resulted in treatment outcomes comparable to continuous 150 mW/cm² irradiance and no or minimal pain during either of the irradiance portions¹¹. These findings, which were restricted to small and single superficial BCC lesions, were further validated by the retrospective review of patients with larger, multiple BCC and Bowen's disease lesions treated with the 2-step approach¹². This review revealed 40-50 mW/cm² to be the highest pain-minimalizing initial irradiance.

In recent years, the topical PDT treatment approach for dermatologic applications had shifted, especially in Europe, towards the use of methyl aminolevulinate (MAL) and a light-emitting diode (LED) irradiation system. The prescribed MAL-PDT protocol calls for two treatments, each at an irradiance of 75 mW/cm² and a light dose of 37 J/cm², with pain during light treatment still being a side effect^{1;13;14}. Therefore, the aims of this study were to determine the pain levels and clinical efficacy of a two-step protocol of MAL-PDT that was designed for illumination by the LED device.

Materials and Methods

This prospective study, carried out at RPCI between April 2011 and July 2012, investigated the use of a two-step irradiation protocol adapted to MAL-PDT, employing laser to determine the irradiance-dependent pain threshold or an LED light source for PDT of superficial BCC (sBCC). The primary and secondary endpoints were pain assessment during irradiation and lesion response. All procedures were approved by the Institutional Review Board. Written informed consent was obtained from all patients.

Twelve patients were men, 9 women, mean age 62 (range 33-78) years, caucasian, with histologically verified diagnosis of sBCC. Patients with multiple lesions could contribute 2 lesions per treatment session. The remaining lesions were treated with non-protocol PDT. Of the 25 lesions treated, 24 were primary and 1 recurrent. Mean lesion diameter was 1.18 cm (range 0.5-2.0). Fourteen lesions were located on the trunk/neck, 10 on extremities, and 1 on the face. Patients with known photosensitivity diseases, hypersensitivity to porphyrin, intolerance to MAL cream ingredients or who were treated with a systemic photosensitizer in the prior 4 months were excluded from study.

Lesions size and location were described and lesions were prepared as described previously ⁷. MAL cream (Metvixia®, Galderma Laboratories, Ft. Worth, TX), containing 160 mg/g of MAL, was applied for 3 h. Lesions were evaluated for fluorescence prior to treatment.

Laser illumination (ArDL, Coherent Innova 100+®, Coherent, Inc., Santa Clara, CA; 633±3 nm) consisted of an initial irradiance (step 1) at 40 (5 lesions) or 50 (10 lesions) mW/cm² until 90±10% of PpIX was photobleached, followed by irradiance at 70 mW/cm² (step 2). The irradiance that caused no more than 3 instances of moderate pain among 10 lesions was considered the threshold irradiance for pain. For LED illumination (Aktelite CL128®, Galderma Laboratories; 570-670 nm) of 10 lesions the addition of a neutral density (ND) filter (Norman ND-10, item NR4350, Calumet Photographic, <http://www.calumetphoto.com/product/NR4350/>) yielded a step-1 irradiance of 35 mW/cm² and step 2 irradiance of 70 mW/cm² after removal of the ND (Figure 1). Lesions received a single exposure to a standard dose of 75 J/cm² ¹².

Patients were randomized to either laser or LED to assure unbiased distribution of lesions among the different study cohorts. In patients who contributed two lesions at a given treatment session, one lesion was treated with the light source according to the randomization scheme, the second with the other light source. Photobleaching of PpIX was monitored for laser irradiation by a non-contact probe ⁶ and for LED irradiation by a hand-held contact probe ¹³.

The maximum pain score was recorded for each irradiance step, using an 11-point pain visual analog scale (VAS). Pain was graded as 0-3 (no to low), 4-6 (moderate) and 7-10 (severe). VAS 4 was considered an irradiance-limiting toxicity. Patients were questioned at the start of treatment and every 5 minutes thereafter about changes in pain and were advised to notify the staff of any changes in their pain at other times.

Follow-up was 6 months (8 lesions), 12 months (9 lesions) and 24 months (8 lesions). Results were described as complete clinical response (CCR, 100% clearance), partial response (PR, >50% clearance), marginal response (MR, <50% clearance), and complete failure (CF, no response). Determinations of CCR required at least 6 months follow-up. Patients with responses other than CCR were either retreated with MAL-PDT or underwent surgery.

Statistical analyses were primarily descriptive. A $P<0.05$ was considered significant. Statistical calculations were done using GraphPad InStat (ver.3.10; GraphPad Software, Inc).

Results

A total of 21 patients with sBCC, participated in the study; 12 men and 9 women, 4 of whom provided 2 lesions, for a total of 25 lesions. Twenty four lesions were primary, 1 was recurrent after previous ALA PDT. Fifty six percent of lesions were located on the trunk/neck, 40 % on the extremities and 4% on the face. Lesion diameters ranged from 0.5 to 2 cm. All lesions received a single treatment for evaluation of pain levels and response.

Laser irradiance at initial 40 mW/cm² followed by 70 mW/cm² yielded a mean VAS of 1.2 (range 0-2) for both the 1st and 2nd irradiance steps. The mean light dose required to reach 90% photobleaching of PpIX was 7.0±1.5 J/cm² (median 6.0 J/cm², range 4.0-12). Escalation of the initial irradiance to 50 mW/cm² resulted in a mean VAS of 1.3 (range 0-4) for the 1st step and 1.9 (range 0-4) for the 2nd step. There were 3 instances of VAS 4 in this cohort of 10 lesions, one in the 1st step and two in the 2nd step. The mean light dose at 50 mW/cm² irradiance required to reach 90% photobleaching of PpIX was 7.7±1.4 J/cm² (median 7.0 J/cm², range 1.0-16).

LED illumination of 10 lesions resulted in a mean VAS 0.2 (range 0.0-1.0) for the 1st step (35 mW/cm²) and 0.5 (range 0.0-2.0) for the 2nd step (70 mW/cm²). The mean light dose required to reach 90% photobleaching of PpIX was 11.4±2.0 J/cm² (median 9.0 J/cm², range 6.0-26).

Treatment times to deliver the total light dose of 75J/cm² for the 3 cohorts were as follows: laser 40/70 mW/cm² – mean 18.87 ±0.32 SE, median 18.72, range 18.28-20.00; laser 50/70 mW/cm² – mean 18.62±0.17 SE, median 18.55, range 17.81-19.43; LED 35/70 mW/cm² – mean 23.52±2.01 SE, median 21.26, range 15.48 –34.52. In the 40/70 mW/cm² laser cohort (5 lesions) there were 3 CCR (60%) at 24 months, with 2 PRs at 6 months. In the 50/70 mW/cm² laser cohort (10 lesions), 80% of lesions showed a CCR at 6 and 12 months, with 2 PRs at 6 months. In the 35/70 mW/cm² LED cohort, 90% of lesions had a CCR at 12 and 24 months, with 1 PR at 6 months. All PR lesions were taken off protocol and treated with additional PDT or surgery. There was 1 recurrence in the 35/70 mW/cm² LED cohort at 24 months after an initial CCR at 12 months. Cosmetic results were good to excellent with 90% of lesions showing slight or moderate hypopigmentation.

Discussion

The introduction of a two-step irradiance protocol for ALA-PDT that eliminates or minimizes the illumination -associated pain represents a new paradigm for the topical application of PDT for non-melanoma skin lesions^{11;12}. It was the goal of the current prospective study to a) determine the irradiance-limiting pain threshold of MAL-PDT and b) to adapt the two-step protocol to the non-laser light source that is commonly used for PDT, thereby creating a simple, inexpensive alternative to conventionally applied topical PDT. Most importantly, this approach spares patients the administration of pain-relieving measures^{16; 17}.

The pain levels of MAL-PDT have been variously described⁴ as less severe^{5;6;18} than or equal^{7;8} to ALA-PDT. The experience from this and our earlier studies¹² indicates comparable irradiance-dependent pain thresholds that lie between 40 and 50 mW/cm² for ALA and MAL-PDT.

Irradiance (fluence rate) has been a subject of intense investigation in PDT, especially with regard to its critical influence on tissue (tumor) oxygenation during light delivery^{19;20}. Langmack et al.²¹, in an ALA-PDT study of sBCC, employing a very low irradiance of 7 mW/cm² for only 12.6 J/cm², reported excellent outcomes with 84% CCRs at 1 year.

Although pain was not quantified, 90% of patients tolerated the treatment without analgesics. Ericson et al.²², treating actinic keratoses with ALA-PDT by using irradiances between 30 and 75 mW/cm² for a total of 40 J/cm², reported improved outcomes at the 30 mW/cm² irradiance, but surprisingly found no significant difference in pain levels at the different irradiances. Wiegell et al. reported reduced pain when treating acne with MAL-PDT with a low irradiance of 34 mW/cm² compared to 68 mW/cm², pointing out the dependence of pain level on both irradiance and the degree of PpIX fluorescence, pain increasing with increasing irradiance and PpIX fluorescence. Thus, it is noted that pain is strongest at the beginning of light delivery, before PpIX is degraded through photobleaching^{13;22}. This observation was the basis for the development of the two-step irradiance protocol introduced by Cottrell et al.¹¹ for ALA-PDT.

We have now validated this approach for MAL-PDT and have adapted the method to the LED light device. Not only were the treatments with the LED device (low irradiance portion 35 mW/cm², high irradiance portion 70 mW/cm²) essentially pain-free, but clinical outcomes were comparable to conventional MAL-PDT delivery¹⁵. Limitations of this study include the overall small number of lesions and the distribution of lesions. Of the 10 BCCs treated in the LED group, only one was located on the face. Since treatment related pain may differ per location, future studies investigating the effectiveness of the 2 step protocol should include larger cohort size in particularly sensitive areas.

Non-invasive, topical PDT, using either ALA or MAL as photosensitizer pro-drug, has proven to be a selective, cosmetically equal or superior alternative to some other treatment modalities^{23; 24} for the treatment of sBCC. This could be especially beneficial for patients with Nevroid Basal Cell Carcinoma syndrome, where numerous and extensive lesions occur early and throughout life^{25; 26} and who may not be candidates for Vismodegib treatment. Clinical outcomes of MAL-PDT also compare favorably with imiquimod therapy²⁷. Several analyses also have shown MAL-PDT to have a cost advantage over surgery or imiquimod^{27; 28; 29}.

The two step irradiance approach described here has the advantage of pain mediation while allowing higher light doses to be delivered without undue prolongation of treatment times and virtually without added costs. Further similar studies in selected groups of patients, such as solid organ transplant patients who can experience more treatment related pain would be of great interest.

Acknowledgments

Supported by NCI grants P01CA55791, P30CA16056, and a grant from the Roswell Park Alliance.

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Figure 1.

The Aktilite LED head with the custom neutral density sheet filter mount in place, photographed from below. A 50% transmission sheet of neutral density film was inserted during the initial low irradiance treatment interval by sliding it into the frame and holding it in place by a paper clip. The mounted film was removed during the higher irradiance interval, enabling the full 70 mW/cm² irradiance to be delivered to the skin surface.